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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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WIGGIN AND DANA LLP
ATTENTION: PATENT DOCKETING
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EXAMINER	
KATAKAM, SUDHAKAR	

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1621	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/593,927	GARCIA COLLAZO ET AL.	
	Examiner	Art Unit	
	SUDHAKAR KATAKAM	1621	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 November 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-19* is/are pending in the application.

4a) Of the above claim(s) *7,8,11,12 and 14* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6,9,10,13 and 15-19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *6/29/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Response to Restriction

1. Applicant's election of claims 1-6, 9-10, 13 and 15-19 in the reply filed on 27 Nov 2009 is acknowledged.

Claims 7, 8, 11, 12 and 14 are withdrawn from consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected species, there being no allowable generic or linking claim.

Election was made **without** traverse in the reply filed on 27 Nov 2009.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 1-6, 9, 10, 13 and 15-19 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a compound of formula (I) or its pharmaceutically acceptable ester, amide or salt, does not reasonably provide enablement for "pharmaceutically acceptable solvate of a compound of formula (I)" as claimed. The claims contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art of medicinal chemistry to use the invention.

As stated in the MPEP 2164.01 (a), "There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a

disclosure does not satisfy the enablement requirement and whether any necessary experimentation undue".

In *In re Wands*, 8 USPQ2d 1400; CAFC, 1988, factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112 first paragraph, have need described. They are:

1. The nature of the invention,
2. The state of the prior art,
3. The predictability or lack thereof in the art,
4. The amount of direction or guidance present,
5. The presence or absence of working examples,
6. The breadth of the claims,
7. The quantity of experimentation needed, and
8. The level of the skill in the art.

(1). **Nature of the invention**: The claimed invention is drawn to a compound of formula (I) or its pharmaceutically acceptable ester, amide, salt or solvate.

(2). **Breadth of the claims**: The claims are extremely broad. The breadth of the claims includes all of the hundreds of thousands of compounds of formula (I) as well as the presently unknown list of solvents embraced by the term "solvate".

(3). **State of the Prior Art**: The term "solvate" found in the claims 1, 3, 4 and 9 is defined as a compound formed by salvation. It has been estimated that approximately one-third of the pharmaceutically active compounds are capable of forming crystalline hydrates. Predicting the formation of solvates or hydrates of a compound and the number of molecules of water of solvent incorporated into the crystal lattice of a compound is complex and difficult. Each solid compound responds uniquely to the possible formation of solvates or hydrates and hence generalizations cannot be made for a series of related compounds [see Vippagunta et al].

(4). **Unpredictability of the Art**: The state of the art is that is not predictable whether solvates will form or what their composition will be. In the language of the physical chemist, a solvate of organic molecule is an interstitial solid solution. This phrase is defined in the second paragraph on page 358 of West (Solid State Chemistry). West, Anthony R., "Solid State Chemistry and its Applications, Wiley, New York, 1988, pages 358 & 365. The solvent molecule is a species introduced into the crystal and no part of the organic host molecule is left out or replaced. In the first paragraph on page 365, West (Solid State Chemistry) says, "it is not usually possible to predict whether solid solutions will form, or if they do form what is their compositional extent". Thus, in the absence of experimentation one cannot predict if a particular solvent will solvate any particular crystal. One cannot predict the stoichiometry of the formed solvate, i.e. if one, two, or a half a molecule of solvent added per molecule of host. In the same paragraph on page 365 West (Solid State Chemistry) explains that it is possible to make meta-stable non-equilibrium solvates, further clouding what Applicants mean by the word solvate. Compared with polymorphs, there is an additional degree of freedom to solvates, which means a different solvent or even the moisture of the air that might change the stabile region of the solvate.

(5). **Amount of Guidance Provided**:

With reference to pharmaceutically acceptable solvates, there is no direction of guidance present in the specification that defines or relates what solvates are being included in the elected invention.

(6). **Presence or Absence of Working Examples**:

There are no working examples of "solvates of a compound of formula (I) in the specification.

(7). **Ordinary Skill in the Art**: The ordinary skill in the art is high.

(8). **Amount of Experimentation Necessary**:

In light of the state of art, the unpredictability of the art and amount of guidance provided, as discussed above, the amount of experimentation necessary to practice the current methods is undue. While the level of the skill in the pharmaceutical art is high, the quantity of experimentation needed is undue experimentation. One of skill in the art would need to prepare compounds with various solvents, reaction conditions, temperature, starting materials without any direction as to what compounds form solvates with which solvent.

Thus, it can safely be concluded that the instant disclosure fails to provide an enabling disclosure for the pharmaceutically acceptable solvates of a compound of formula (I). Therefore, the claims 1, 3, 4 and 9, and their dependents, contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art of medicinal chemistry to use the invention.

4. Claims 6, 13, are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treatment of conditions that were known to be treatable using established TR ligands, does not reasonably provide enablement for the treatment or prophylaxis of all diseases or disorders associated with thyroid receptor. The specification does not enable any person skilled in the art to which it pertains, or

with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

To be enabling, the specification of the patent must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation. In re Wright, 999, F.2d 1557, 1561 (Fe. Cir. 1993). Explaining what is meant by "undue experimentation," the Federal Circuit has stated:

> The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed to enable the determination of how to practice a desired embodiment of the claimed invention. PPG v. Guardian, 75, F.3d 1558, 1564 (Fed. Cir. 1996).1

The factors that may be considered in determining whether a disclosure would required undue experimentation are set forth by In re Wands, 8 USPQ2d 1400 (Fed. Cir., 1988) at 1404 where the court set forth the eight factors to consider when assessing if disclosure would have required undue experimentation. Citing Ex parte Forman, 230 USPQ 546 (BdsApls 1986) at 547 the court recited eight factors:

1) the nature of the invention;
2) the breadth of the claims;
3) the predictability or unpredictability of the art;
4) the amount of direction or guidance presented;
5) the presence or absence of working examples;
6) the quantity of experimentation necessary;
7) the state of the prior art; and,
8) the relative skill of those skilled in the art.

These factors are always applied against the background understanding that scope of enablement varies inversely with the degree of unpredictability involved. In re Fisher, 57 CCPA 1099, 1108, 427 F.2d 833, 839, 166 USPQ 18, 24 (1970). Keeping

that in mind, the Wands factors are relevant to the instant fact situation for the following reasons:

1) The nature of the invention, state and predictability of the art, and relative skill level

The invention relates to treatment or prevention of a disease or disorder associated with thyroid receptor activity in mammal. The relative skill of those in the art is high, that of an MD or PhD. That factor is outweighed, however, by the unpredictable nature of the art. As illustrative of the state of the art, the examiner cites *Potential therapeutic applications of thyroid hormone analogs*. Brenta G, Danzi S, Klein I. Nat Clin Pract Endocrinol Metab. 2007 Sep;3(9):632-40. Review PMID: 17710084 [PubMed - indexed for MEDLINE].

2) The breadth of the claims

Since the instant specification provides no limiting definition of the term "prophylaxis" and "treating all diseases associated with thyroid receptor activity", the term will be interpreted expansively. The term "prophylaxis" may vary widely in meaning, from "preventing" a disease from occurring to "preventing" it from progressing. Nor is the term limited by any time frame.

The claims are thus very broad insofar as they suggest that one will not experience the disease when taking the claimed agent; that should one get the disease, it will not worsen; or that following its treatment, it will not recur. While such "prevention" might theoretically be possible under strictly controlled laboratory conditions, as a

practical matter it is nearly impossible to achieve in the "real world" in which patients live.

3) The amount of direction or guidance provided and the presence or absence of working examples

The specification provides no direction or guidance for practicing the claimed invention in its "full scope". No reasonably specific guidance is provided concerning useful therapeutic protocols for preventing or treating a diseases or disorders associated with thyroid receptor activity in mammals, other than administration. The latter is corroborated by the working examples.

The teachings at pages 58-60 are suggestions as to what assays someone could do if they wanted to determine what the biological activity is. The specification does disclose on page 58 that the compounds bind to the TR receptor. Page 34-35 gives a long list of conditions to be treated. These clearly have not enabled that genus.

4) The quantity of experimentation necessary

Because of the known unpredictability of the art, and in the absence of experimental evidence, no one skilled in the art would accept the assertion that the instantly claimed agents could be predictably used to prevent a disease or disorder associated with thyroid receptor activity as inferred by the claim and contemplated by the specification. Accordingly, the instant claims do not comply with the enablement requirement of §112, since to practice the claimed invention in its "full scope" a person of ordinary skill n the art would have to engage in undue experimentation, with no assurance of success.

5) Suggested alternative language

Since the term "prophylaxis" is inclusive of various administrative timing schemes and thus provides adequate coverage for all reasonably successful therapies (prophylactic or active), the examiner recommends deleting the term "prophylaxis" and simply reciting "treatment" only instead. Also limit the treatment of conditions that were known to be treatable using established TR ligands but not more than that.

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 1-6, 9, 10, 13, 15-19 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim subject matter which applicant regards as the invention.

In claims 1, 3, 4 and 9, it is unclear the "ester or amides" of "what compound", applicants intended to encompass. Therefore, it is impossible to determine the metes and bounds of the claimed subject matter. The claims 1, 3, 4 and 9, and their dependent claims are, therefore, rendered indefinite.

In the claims 1-4 recited "portions of groups optionally being substituted", however, it is unclear from the claim language, which groups are being substituted on the formula (I). Therefore, it is impossible to determine the metes and bounds of the claimed subject matter. The claims 1-4 and their dependent claims are, therefore, rendered indefinite.

The claim 5 is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced. Therefore, it is impossible to

determine the metes and bounds of the claimed subject matter. The claim 5 and its dependent claims are, therefore, rendered indefinite.

The claim 4 recites the limitation "suitable" in the claim language. It is unclear, what are the suitable leaving groups or suitable bases from the claim language. Therefore, it is impossible to determine the metes and bounds of the claimed subject matter. Claim 4 is therefore rendered indefinite.

The claim 15 recites "derivative", which renders the claim indefinite because it is unclear what compound applicant is intending to encompass.

Conclusion

7. No claim is allowed.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sudhakar Katakam whose telephone number is 571-272-9929. The examiner can normally be reached on M-F 8:30 AM - 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Daniel Sullivan can be reached on 571-272-0779. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic

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/Sudhakar Katakam/
Examiner, Art Unit 1621